Treatment of locally advanced stage (stage III)

- All patients planned for definitive stage III NSCLC treatment should undergo a diagnostic contrast-enhanced CT scan of the chest and upper abdomen followed by a PET or a combined PET-CT with a CT technique with adequately high resolution for initial staging purposes [I, A] in order to rule out detectable extrathoracic, extracranial metastasis, and to assess potential mediastinal lymph node involvement, ideally within 4 weeks before the start of treatment [III, B]. Single PET-positive distant lesions need pathological confirmation [V, B].
- For patients with operable N2 disease, pathological staging of the mediastinum is advised [III, C].
- All patients planned for curative stage III NSCLC treatment should receive brain imaging for initial staging [III, B]. Contrast-enhanced brain MRI is the preferred method for staging of the brain in stage III disease [III, A]. If it is not possible to perform MRI, dedicated contrast-enhanced brain CT scan is advised [III, B].

Resectable LA-NSCLC

- If, despite adequate mediastinal staging procedures, N2 disease is only documented intra-operatively, surgery should be followed by adjuvant ChT [I, A].
- In case of complete resection, addition of PORT is not routinely recommended, but may be an option following individual risk assessment [V, C].
- If single station N2 disease can be demonstrated by preoperative pathological nodal analysis, resection followed by adjuvant ChT, induction ChT followed by surgery or induction CRT followed by surgery are options. If induction ChT alone is given preoperatively, PORT is not standard treatment, but may be an option based on critical evaluation of locoregional relapse risks [IV, C].
- In multistation N2 or N3, concurrent definitive CRT is preferred [I, A]. An experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision, including the role of surgery in these cases [IV, C].
- In potentially resectable superior sulcus tumours, concurrent CRT induction followed by definitive surgery is the treatment of choice [III, A]. The same strategy may be applied for potentially resectable T3 or T4 central tumours in highly selected cases and experienced centres [III, B]. In both situations, surgery should be carried out within 4 weeks after the end of RT [III, B].

Systemic therapy

- For curative-intent management, patients should be able to undergo platinum-based ChT (preferably cisplatin) [I, A].
- (Neo)adjuvant anti PD(L)-1 checkpoint inhibitors are currently being evaluated in addition to current standard of care.
- Checkpoints are also being evaluated after CRT as consolidation therapy.

Unresectable LA-NSCLC

- Concurrent CRT is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent CRT is not possible—for any reason—sequential ChT followed by definitive RT represents a valid and effective alternative [I, A].

- There is no role for prophylactic cranial irradiation in stage III NSCLC [II, A]. In the absence of contraindications, the optimal ChT to be combined with radiation in stage III NSCLC should be based on cisplatin. There are no firm conclusions supporting single-agent carboplatin as a radiation sensitiser [I, A].
- Most comparative studies of concurrent CRT versus sequential administration were using cisplatin-etoposide or cisplatin-vinca alkaloid (typically: cisplatin-vinorelbine), or cisplatin-pemetrexed if non-squamous histology. There are no comparative phase III trials using the paclitaxel/carboplatin regimen. When delivered perioperatively cisplatin-based combinations are considered the treatment of choice, in the absence of contraindications [I, A].
- In the stage III disease CRT strategy, two to four cycles of concomitant ChT should be delivered [I, A]. There is no evidence for further induction or consolidation ChT. In the perioperative setting, three to four cycles of cisplatin-based ChT are recommended [I, A], aiming at a total cumulative dose of at least 300 mg/m2 of cisplatin [II, B].
- 60–66 Gy in 30–33 daily fractions is recommended for concurrent CRT [I, A]. Maximum overall treatment time should not exceed 7 weeks [III, B]. 'Biological intensification', such as treatment acceleration, is not standard practice in concurrent CRT schedules [III, B].
- In sequential approaches, RT delivered in a short overall treatment time is recommended [I, A].